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Recent Developments in Samarium Diiodide Promoted Organic Reactions

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In memory of Hans Wynberg

ABSTRACT: In the early eighties, we introduced samarium diiodide for the transformation of various functional groups. Since then, this reducing agent has been extensively used for the reductive cleavage of single bonds, C-C bond formations, C-N bond formations, and β-elimination reactions. In this Personal Account, we highlight our initial results, as well as some of the contributions from various research groups. Because of space limitations, we arbitrarily select some useful results that have recently been described in literature. **DOI 10.1002/tcr.201200028**

Keywords: dimerization, electron transfer, radical reactions, reduction, samarium

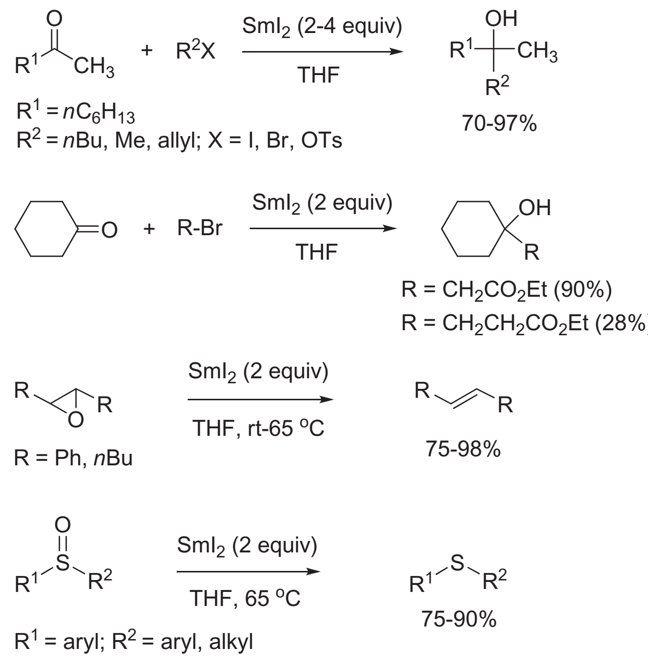
1. Introduction

Samarium is an element of the lanthanide family and it was first isolated as an impure salt in 1879 by Lecoq de Boisbaudran.[1] The name of this element is derived from the name of the mineral Samarskite. Samarium diiodide was first prepared in 1906 by Matignon and Caze by the disproportionation of samarium triiodide at 800 °C.[2] The reduction potential of Sm^{2+} ($Sm^{2+} \rightarrow Sm^{3+}$) was evaluated to be around -1.55 V,[3] which means that SmI_2 should behave as a good monoelectronic donor. In 1975, we became interested in the possibility of performing organic transformations that were mediated by lanthanides.[4] Oxidations with Ce^{IV} were well-known and some catalytic transformations in the presence of Ln^{III} had already been described, but there were almost no reports on the possible use of Ln^{II} compounds as reducing agents. We noticed that an aqueous solution of $EuCl_2$ had been used to reduce isonicotinic acid into its corresponding aldehyde.[6] However, we couldn't find any further examples of Eu^{II}, which is a weak monoelectronic donor (E_0 = -0.42 V for $Eu^{2+} \rightarrow Eu^{3+}$), as a reducing agent. Eventually, Yb^{2+} and Sm^{2+} compounds were studied as reducing agents for organic compounds. YbI_2 and SmI_2 were selected because of their ease of preparation and because of their partial solubility in THF. We devised a simple preparation of these salts by treating Yb or Sm metals (as powders) with an iodine donor, such as 1,2-diiodoethane. These reactions are very smooth at room temperature and generate ethylene as a by-product. This approach for the preparation of YbI_2 and SmI_2 was published in 1977.[7] Many variations of this preparation have since been described by changing the iodine source and the solvent.[8,9] The lanthanide diiodides that are prepared in this way are solvated by THF molecules; the X-ray crystal structure of $SmI_2(THF)_5$ has been described by Evans et al.[10]

A preliminary screening of the properties of these iodides was easy to perform because of the color change of the solutions (for the $Ln^{2+} \rightarrow Ln^{3+}$ transformation). It soon became evident that SmI_2 was the most useful reagent when compared to EuI_2 and YbI_2. TmI_2 was expected to be a stronger reducing agent because it is characterized by E_0 = -1.30 V. However, its study was excluded because it was very expensive.[11] In a note in 1977 and then in a full paper in 1980, we reported some chemical transformations of various classes of organic compounds that were induced by samarium diiodide.[7,8] These initial results were quite promising and justified our own work and the subsequent investigations of many groups in this area.

1.1. The Initial Screening of Some Reactions that were Induced by Samarium Diiodide

It soon became obvious that SmI_2 was able to act as a reducing agent for many substrates and for several types of transformations, as shown in Scheme 1. A mixture of an organic halide and a ketone in the presence of two equivalents of SmI_2 in THF gave, in many cases, tertiary alcohols; this reaction was named the samarium Barbier reaction, because SmI_2 plays the role of the metal in the Barbier procedure.[7,8] Aliphatic aldehydes are not good components in the samarium Barbier reaction because the samarium(III) alcoholate that is initially formed acts as a catalyst in an Oppenauer oxidation of the aldehyde. The ketone that is generated reacts further in a Barbier reaction, finally giving a tertiary alcohol.[7] Acid chlorides can react with ketones in a formal Barbier-type reaction. Aldehydes are transformed into pinacols and the reaction is especially fast for aromatic aldehydes.[13] The reduction of carbonyl compounds has been noticed in the presence of proton sources. Organic halides gave rise to reduction into alkanes or to coupling, depending on their structure. Finally, the deoxygenation of some epoxides or sulfoxides has been noticed. All of these above transformations are described in Schemes 1 and 2.

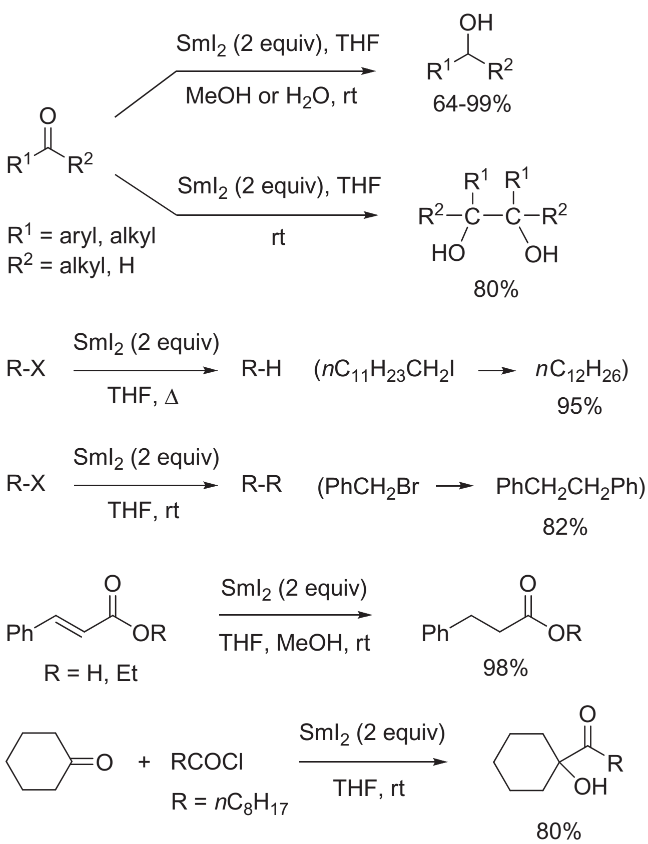


Scheme 1.

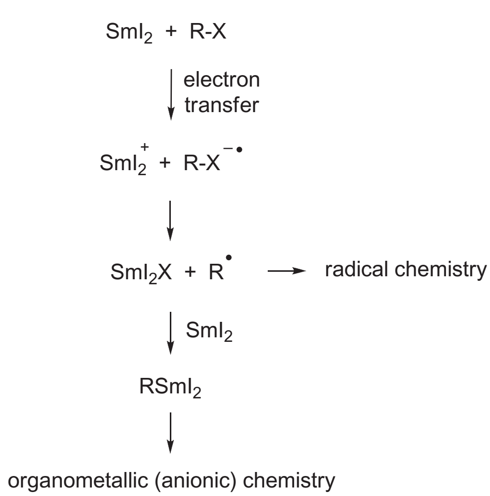
Samarium diiodide acts as a single electron donor towards the organic substrates, thereby initially generating a radical anion species that can evolve in various ways, as shown in Scheme 3. The radical anion of an organic halide will be transformed into a radical, which can give rise to some radical

Henri B. Kagan was born in France in 1930. He prepared his PhD under the supervision of Dr. J. Jacques at the Collège of France, Paris. In 1968, he joined the Université Paris-Sud, Orsay, where he is Emeritus Professor. He is also a member of the French Academy of Sciences. His research interests include asymmetric synthesis, asymmetric catalysis, and the use of lanthanide reagents. He has received numerous awards, including the Prelog Medal, the August-Wilhelm-von-Hofmann Medal, the Nagoya Gold Medal of Organic Chemistry, the Tetrahedron Prize, the Wolf Prize for Chemistry (shared with K. B. Sharpless and R. Noyori), the Grand Prix de la Fondation de la Maison de la Chimie (shared with H. Yamamoto), the Ryoji Noyori Prize, the Bower award of the Franklin Institute, the Horst-Pracejus award, and the Burckhardt Helferich Medal (2011).

Kovuru Gopalaiah was born in Andhra Pradesh (India) in 1976. He obtained his MSc in organic chemistry from Sri Venkateswara University in 1998. Then, he joined the Indian Institute of Science (IISc), Bangalore, where he received his PhD in chemistry in 2005 under the supervision of Prof. S. Chandrasekhar. From 2006–2008, he worked with Prof. Henri B. Kagan at the Université Paris-Sud, Orsay, as a Postdoctoral Fellow. Presently, he is an Assistant Professor at the University of Delhi (India). His research interests are focused on the development of metal-catalyzed organic transformations and asymmetric synthesis.

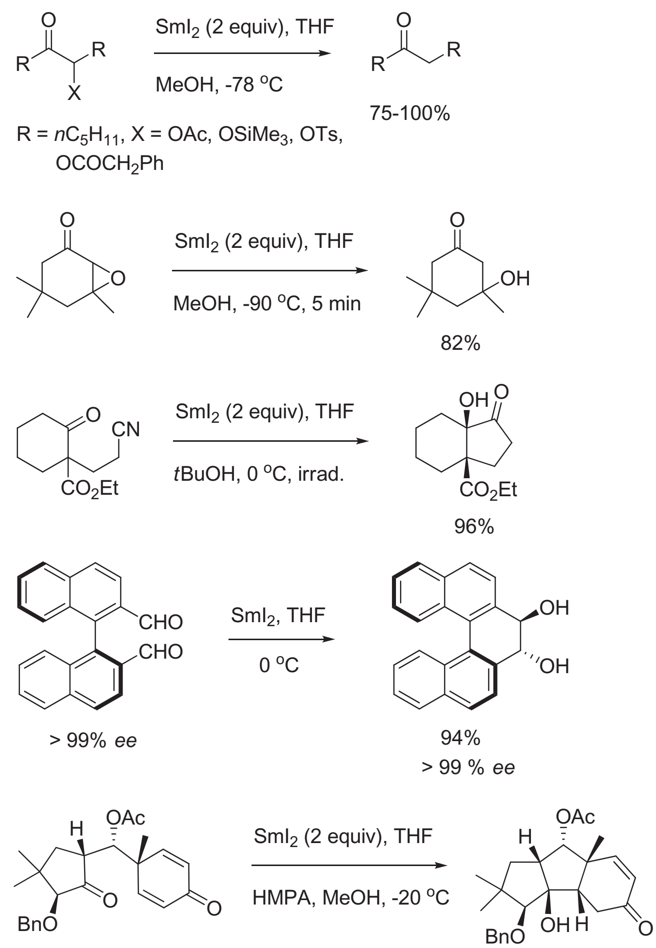


Scheme 2.



Scheme 3.

chemistry. The further reduction of the radical may also generate an organosamarium species in situ. Similarly, a carbonyl compound will initially be transformed into a ketyl radical; its further evolution will depend on the structure and experimental conditions. It is interesting to point out that many reactions could be accelerated by additives such as hexamethylphosphoramide (HMPA)[14] and by Fe^{III} or Ni^{II} salts.[8]



Scheme 4.

The chemistry of SmI_2 has been so-extensively developed since our initial studies in the early 1980s that it is impossible to cover it completely. Following these reports, several transformations, as described in Scheme 4, were soon reported in the literature. Herein, we focus on some of the recently reported developments and trends in SmI_2 chemistry by arbitrarily choosing individual examples; the readers is pointed to many review articles for specific transformations that are induced by samarium diiodide.[15]

2. Functional-Group Transformations

In the early stages of the development of SmI_2 chemistry, we published a few articles on some functional-group transformations that employ SmI_2, as indicated in Schemes 1 and 2. Later,

many research groups extended the utility of samarium diiodide to a variety of organic transformations. Various types of unsaturated compounds have been reduced or modified by using this reagent. The reactivity of samarium diiodide is enhanced by the presence of additives or co-solvents.[14,15h,15m] The mechanisms for several transformations are well-established and will be not discussed herein because of space limitations.

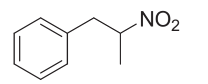
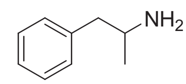
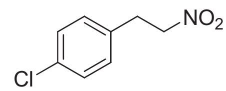
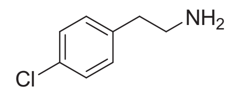
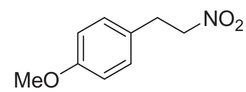
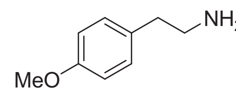
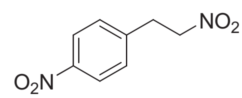
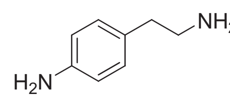
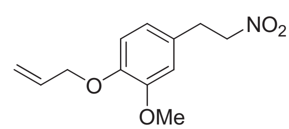
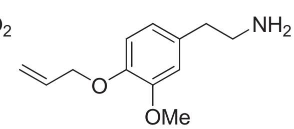
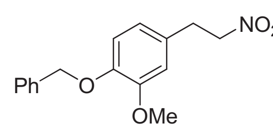
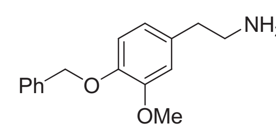
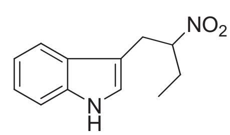
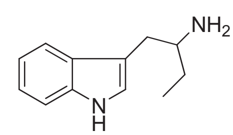
Dahlén and Hilmersson demonstrated the instantaneous SmI_2/water-mediated reduction of ketones into their corresponding alcohols in the presence of amines as additives;[16] mono-, di-, and tridentate amines, such as Et_3N, *N,N,N′,N′*-tetramethylethylenediamine (TMEDA), and *N,N,N′,N″,N″*-pentamethyldiethylenetriamine (PMDTA), respectively, accelerated the reduction reactions by at least 100,000 fold compared to the reduction without a proton source, or at least 100-times faster than the rate of the widely used HMPA/alcohol reduction reactions. The selective reduction of carbon-carbon double bonds of α,β-unsaturated esters and amides with SmI_2/*N,N*-dimethylacetamide was achieved by Inanaga et al.[17] Bidentate ligands, such as 1,2- or 1,3-diamine derivatives, were also effective in the reaction; however no reduction occurred in the presence of PMDTA.

The reduction of nitro groups on aliphatic and aromatic substrates can be performed with SmI_2 or SmI_2/MeOH.[18] These reductions are generally slow and, in some cases, give a complex mixture of coupling products and various reduced products. Hilmersson's group developed an efficient method for the rapid reduction of nitroalkanes (Table 1) and α,β-unsaturated nitroalkenes (Table 2) by using a SmI_2/water/*i*$PrNH_2$ procedure.[19] The α,β-unsaturated nitroalkenes were directly reduced into saturated amines and substrates that contained halide, ether, allyl ether, benzyl, or indole moieties were tolerated under these reduction conditions. Moreover, the utility of this SmI_2/water/amine reagent system has been established for the rapid and selective reduction of alkyl and aryl halides,[20] α,β-unsaturated esters,[21] conjugated olefins,[22] β-hydroxyketones,[23] imines,[24] allyl ethers,[25] and hydrocarbons[26] in up to quantitative yield.

Procter and co-workers also reported the use of the SmI_2/water/amine system for reducing unactivated esters in high yields (Table 3).[27] Their SmI_2/water/Et_3N procedure is very effective for the reduction of esters, diesters, lactones, aromatic esters, coumarins, and heterocyclic esters into their corresponding alcohols (Scheme 5).

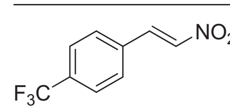
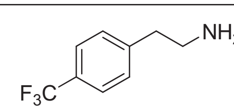
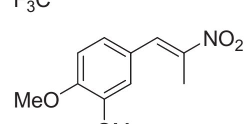
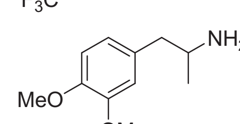
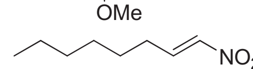
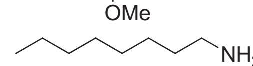
Hirama and co-workers reported a samarium diiodide mediated reductive olefination of vicinal propargylic diol derivatives with the co-existence of an epoxide in the molecule, which is a crucial transformation for the synthesis of the 9-membered epoxydiyne precursor in the kedarcidin chromophore (**1**, Figure 1).[28] Reductive olefination at the C4-C5 position of α-mesylate **2** takes place to produce enediyne **6** and

Table 1. Reduction of nitroalkanes by using the SmI_2/water/*i*$PrNH_2$ system.[a]

Starting Material	Product	Yield (%)
		92
		95
		96
		86
		85
		94
		99

[a]Reaction conditions: SmI_2 (6 mol), H_2O (60 mol), *i*$PrNH_2$(12 mol), THF, rt.

Table 2. Reduction of α,β-unsaturated nitroalkenes into saturated amines.[a]

Starting Material	Product	Yield (%)
		45
		75
		70

[a]Reaction conditions: SmI_2 (8–10 mol), H_2O (80–100 mol), *i*$PrNH_2$(16–20 mol), THF, rt.

its cycloaromatized product **7** in a combined 60% yield (**6**/**7** = 3:2; Table 4, entry 1). In this reaction, the labile 9-membered enediyne **6** first underwent cycloaromatization to give compound **7**. On the other hand, treatment of β-mesylate **3** with

SmI_2 afforded a mixture of enediyne **6** and its cycloaromatized product **7** in 72% yield (Table 4, entry 2). When the crude products were treated with excess 1,4-cyclohexadiene in CH_2Cl_2, cycloaromatized compound **7** was isolated as the sole product. In parallel, the SmI_2-mediated reductive olefination was carried out for C5-acetate **4** and C5-*p*-trifluoromethyl benzoate **5** (Table 4, entries 3 and 4). The reductive olefination is chemoselective and the epoxide functionality survives under these reaction conditions.

Salvinorin A (**11**), a hallucinogenic neoclerodane diterpenoid, was synthesized by using the samarium diiodide mediated double conjugate reduction as a key step in the total synthesis (Scheme 6).[29] The unsaturated lactonic ester **9** that was derived from keto-ester **8** underwent double reduction at the C3 and C7 positions by treating with SmI_2 in the presence of triethylamine and acetic acid in toluene, thereby furnishing lactonic ester **10** as a single diastereomer.

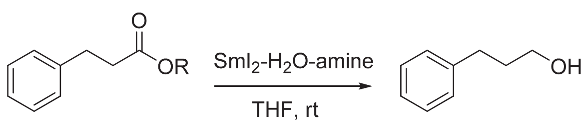
3. Reductive Cleavage of Single Bonds

Samarium diiodide has been extensively employed in mediating the fragmentation of carbon-carbon, carbon-heteroatom, and heteroatom-heteroatom single bonds.[30,15i] Some interesting examples are presented below.

3.1. C-C Bond Fragmentation

This type of transformation commonly takes place in ring-strained systems[31] and in 1,4-diketones.[32] Recently,

Table 3. Reduction of hydrocinnamic esters by using SmI_2/water/amine systems.



Entry	R	Amine	Time (h)	Yield (%)
1	Me	Et_3N	2	97
2	*i*Pr	Et_3N	5	88
3	*t*Bu	pyrrolidine	5	83
4	Ph	Et_3N	2	94
5	Bn	Et_3N	2	97

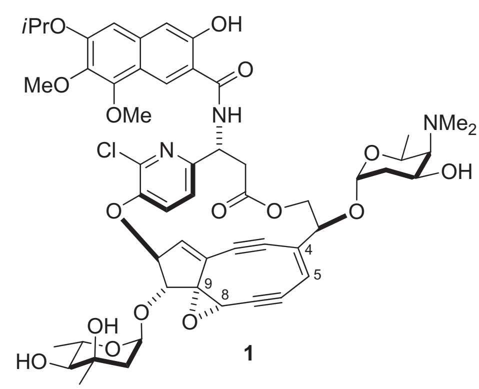
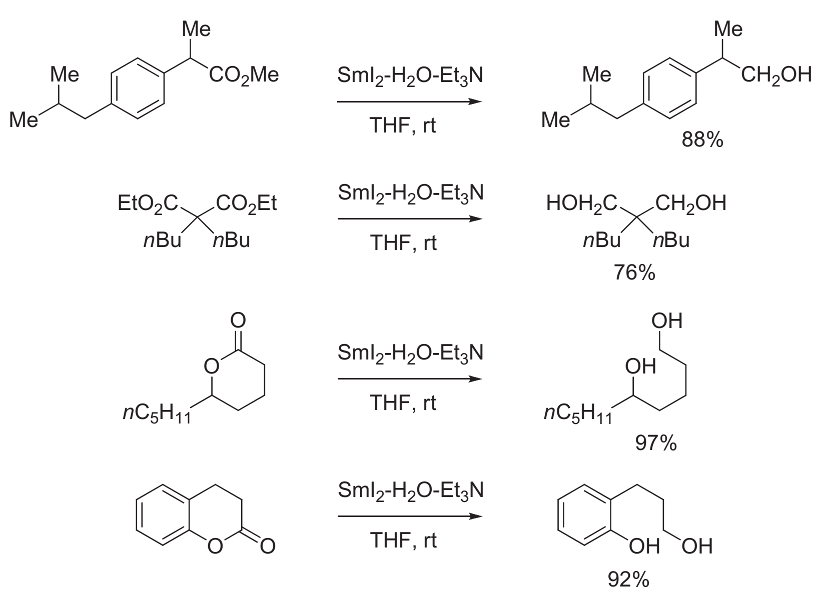


Fig. 1. The structure of the kedarcidin chromophore.



Scheme 5.

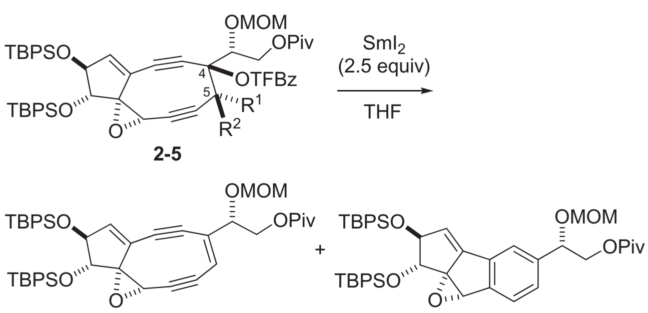
SmI_2-promoted C-C bond fragmentation was reported in α-aminomethyl malonates **12**, a type of strain-free substrate that contains a quaternary carbon center adjacent to the alkoxycarbonyl groups (Table 5).[33] The deaminomethylation products **13** were isolated in excellent yields. The presence of an amino group in the substrate is necessary for the success of the transformation. The proposed mechanism involves a free-radical reaction pathway (Scheme 7). The ketyl radical anion **14** was considered to be a key intermediate in the reaction.

3.2. C-N Bond Fragmentation

Substrates that possess highly strained three- or four-membered nitrogen heterocyclic rings adjacent to a carbonyl group, such as 2-acylaziridines and 4-acylazetidin-2-ones, smoothly undergo reductive cleavage of their carbon-nitrogen bonds in the presence of samarium diiodide.[34] Alternatively, the SmI_2-mediated carbon-nitrogen bond fragmentations proceeds through the reductive removal of the N-substituted benzotriazolyl group[35] or by isonitrile/nitrile rearrangement.[36] Attractive examples of the reductive deamination reaction were reported by Honda and Ishikawa for derivatives of proline (Table 6), 2-acetylpiperidine, and ethyl pipecolinate (Table 7), in which the leaving amino groups are involved in the cyclic systems.[37] Interestingly, reductive deamination also took place in *N*-(2-oxopropyl)phthalimide with SmI_2 in HMPA/THF in the presence of MeOH and gave the phthalimide in 72% yield (Table 7).

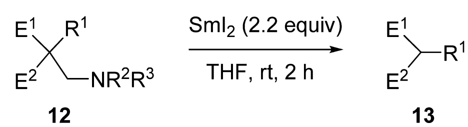
More recently, the SmI_2-promoted reductive deamination reaction was used as a key step in the synthesis of bulgaramine, a member of the benzindenoazepine alkaloids (Scheme 8).[38] Cleavage of the C-N bond in ester **15** with SmI_2 took place in the presence of MeOH as a proton source, thereby giving a secondary amine **16**, which, on treatment with *p*-TsOH monohydrate, furnished benzindenoazepine-type compound **17** directly in 68% yield from compound **15**. A coccinellied alkaloid, (-)-adalinine, has also been synthesized from proline derivative **18** or from pyrrolidin-3-one derivative **19** by using

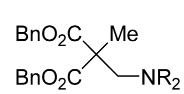
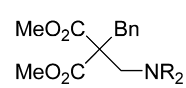
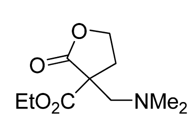
Table 4. Chemoselective reductive olefination mediated by SmI_2.

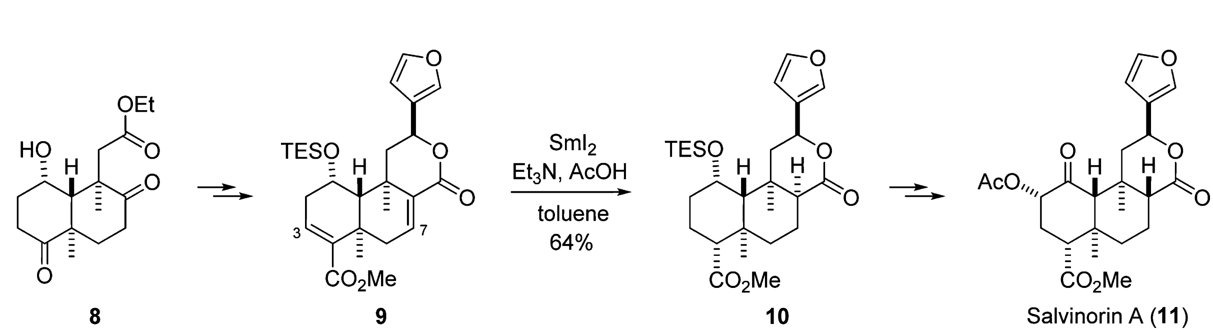


Entry	Substrate	R^1	R^2	Conditions	**6** + **7** Yield (%)
1	**2**	OMs	H	-15 °C, 6 min	60
2	**3**	H	OMs	-20 °C, 10 min	72
3	**4**	OAc	H	0 °C, 17 min	53
4	**5**	H	OTFBz	-15 °C, 8 min	50

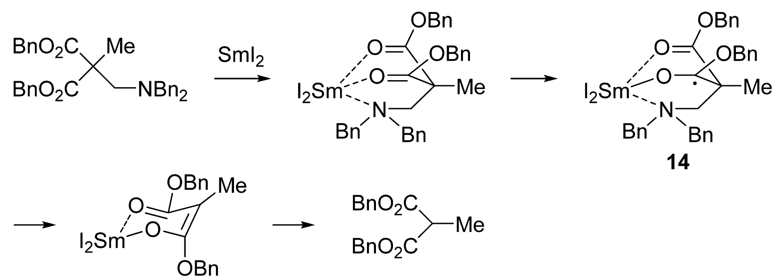
Table 5. SmI_2-mediated carbon-carbon bond fragmentation of malonates **12**.



Substrate		Yield (%)
	R = Me	94
	R = Bn	94
	R, R = -$(CH_2)_5$-	89
	R = Me	90
	R, R = -$(CH_2)_2O(CH_2)_2$-	85
		94

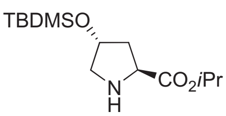
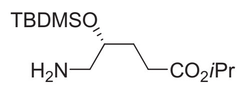
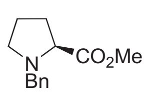
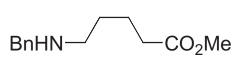
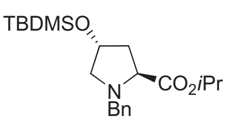
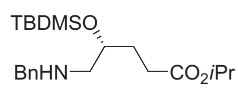


Scheme 6.



Scheme 7.

Table 6. Reductive deamination in proline derivatives.[a]

Starting material	Product	Proton source	Reaction time	Yield (%)
		MeOH pivalic acid	1.5 h 40 min	88 82
		MeOH pivalic acid	9 h 1 h	82 92
		MeOH pivalic acid	7.5 h 45 min	99 88

[a]SmI_2 (5 equiv), proton source (2.5 equiv), HMPA (5 equiv), THF, 0 °C to room temperature.

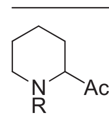
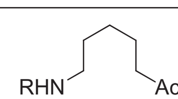
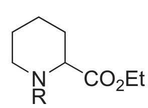
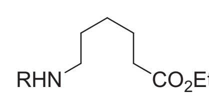
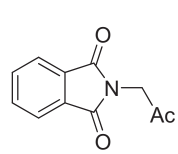
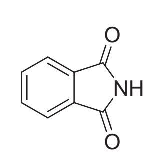
SmI_2-mediated reductive carbon-nitrogen bond cleavage as a key transformation (Scheme 9).[39]

N-substituted β,γ-unsaturated amides **23** are readily accessible by way of SmI_2-mediated reductive cleavage of the C-N bond at the α position of adducts **22**, which are generated from the Ugi reaction of α,β-unsaturated aldehydes **20**, isocyanides **21**, aniline, and acetic acid (Scheme 10).[40]

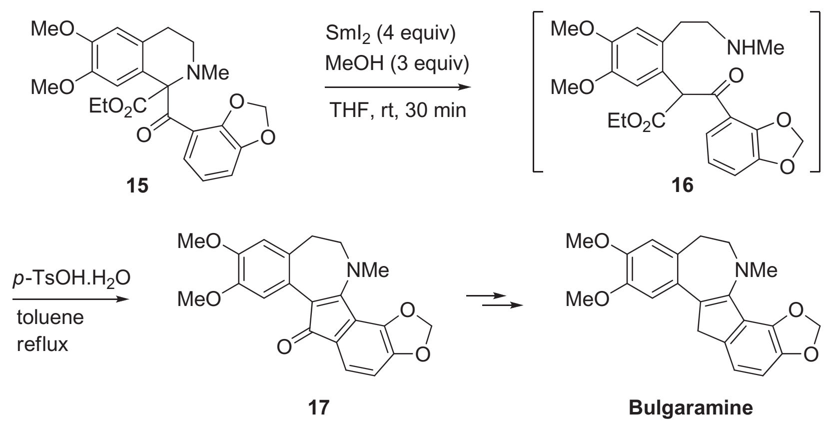
3.3. C-O Bond Fragmentation

Initially, this type of fragmentation reaction was reported for the ring-opening of α-keto cyclic ethers, such as epoxides **24** and tetrahydropyrans **26**, to give their corresponding ring-opened products (**25** and **27**, respectively), based on the trapping agent on the samarium(III) enolate (Scheme 11).[41] In 2003, Hilmersson and co-workers described the SmI_2/water/*i*$PrNH_2$-mediated reductive cleavage of allyl-ether-protected alcohols.[24] At room temperature, several aliphatic allylic ethers and allyl-protected carbohydrates were cleaved to obtain their corresponding alcohols in high yield and with interesting chemoselectivity (Table 8). The authors have also developed

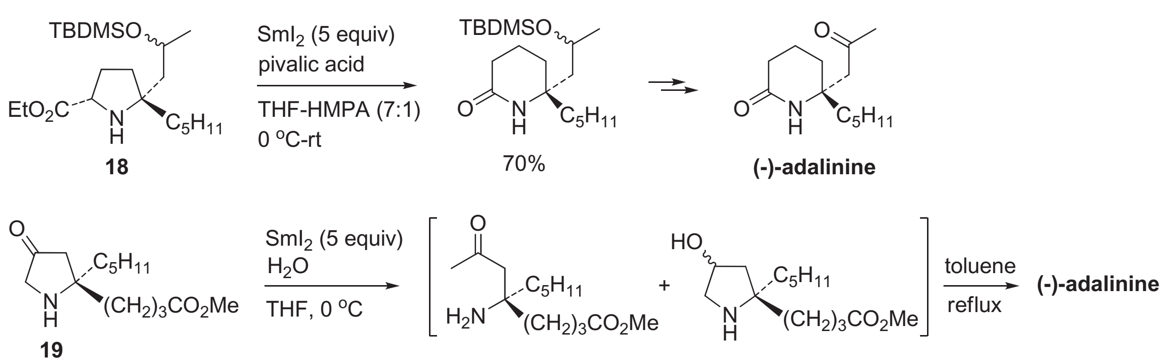
Table 7. Reductive deamination in derivatives of 2-acetylpiperidine, ethyl pipecolinate, and phthalimide.[a]

Starting material	Product	R	Reaction time	Yield (%)
		Me Bn Ac Boc	1 min 1 min 5 min 5 min	87 96 94 96
		Me Bn Ac	5 min 5 min 45 min	86 89 78
		-	1 min	72

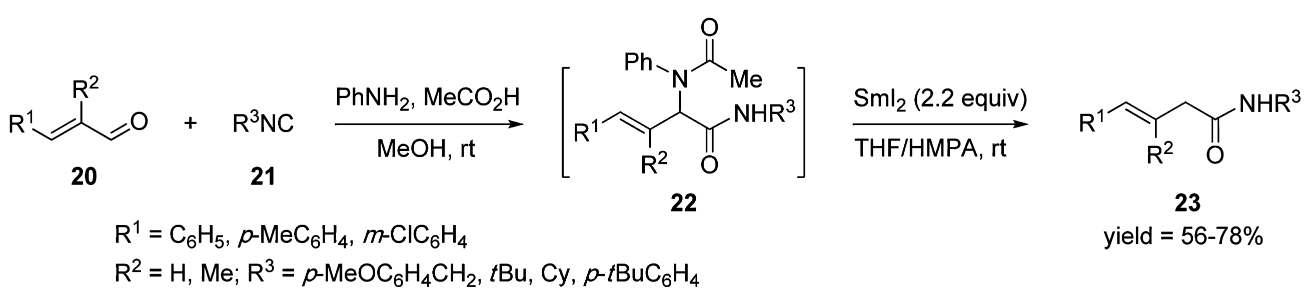
[a]SmI_2 (5 equiv), MeOH (2.5 equiv), HMPA (5 equiv), THF, 0 °C to rt.



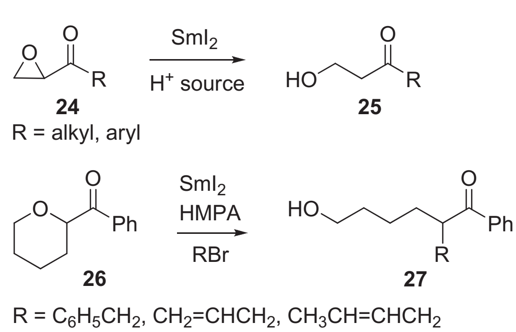
Scheme 8.



Scheme 9. TBDMS=*tert*-butyldimethylsilyl.



Scheme 10.



Scheme 11.

the SmI_2/water/amine-mediated reductive cleavage of benzylic alcohols and 1-phenyl ethanol esters to afford their corresponding deoxygenated products.[42]

The SmI_2/water/*i*$PrNH_2$ procedure was used for the deprotection of various propargyl ethers **28** to afford their corresponding alcohols **29** (Table 9).[43] Acid-sensitive protecting groups methoxymethyl (MOM) and acetonide are stable under these conditions. Furthermore, this method was applied for the synthesis of oligosaccharides (Scheme 12).

Lam and Markó used the SmI_2/HMPA system for the chemoselective reduction of aromatic esters **30** into their cor-

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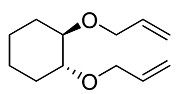
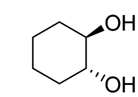
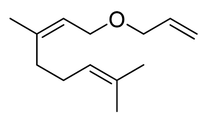
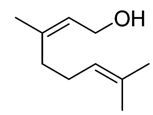
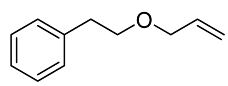
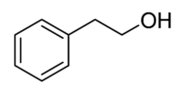
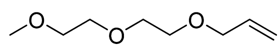
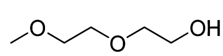
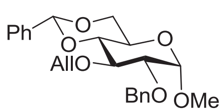
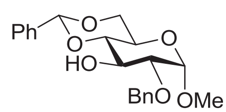
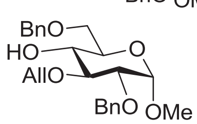
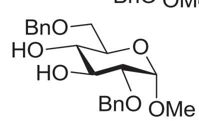
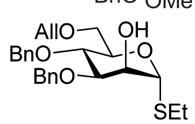
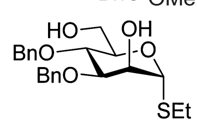
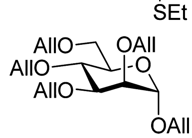
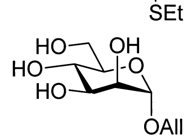
Table 8. Deallylation of various alcohols by using the SmI_2/water/*i*PrNH$_2$ system.

Substrate	Product	Time (min)	Conversion % (Isolated yield %)
		1	>99
		2	>99 (88)
		1	>99 (93)
		1	>99
		2d	(80)
		15	>99 (95)
		5	>99 (95)
		2 h	(81)

responding deoxygenated products **31** (Scheme 13).[44] Only toluates are deoxygenated by using this procedure. On the other hand, a wide range of other functional groups and protecting groups, such as aliphatic esters, silyl ethers, amides, alcohols, acetals, and ketals, are tolerated under the SmI_2/HMPA reaction conditions. Interestingly, when aromatic esters **30** are subjected to the SmI_2/HMPA/MeOH procedure, chemoselective deprotection of the toluates affords alcohols **32** (Scheme 14).[45,46] Then again, several other functional groups and protecting groups are compatible under these reaction conditions.

The first reduction of lactones into diols by using SmI_2/water was reported by Procter and co-workers.[47] This system was selective for the reduction of lactones over esters and it displayed complete ring-size selectivity, with only six-membered lactones converted into their corresponding diols (Scheme 15). On the basis of experimental and computational studies, it was suggested that the selectivity originated from the initial electron transfer to the lactone carbonyl group. The same group also described the SmI_2/water-mediated reduction of cyclic 1,3-diesters **33** into 3-hydroxy acids **34** (Table 10).[48] This SmI_2/water procedure was selective for cyclic 1,3-diesters over acyclic 1,3-diesters, esters, and some lactones. Competitive experiments were performed to illustrate the selectivity for cyclic 1,3-diesters over esters and acyclic 1,3-diesters (Scheme 16).

β,γ-Unsaturated amides **36** are easily synthesized by way of SmI_2-mediated reductive cleavage of the α-heteroatom-carbon bonds in adducts **35**, which are generated from the three-component Passerini reaction of α,β-unsaturated aldehydes, isocyanides, and acids (Scheme 17).[49]

3.4. N-O Bond Fragmentation

A detailed study of the reductive cleavage of N-O bonds by using samarium diiodide has been reported by Keck et al. for hydroxylamines and hydroxamic acid derivatives.[50] Subsequent quenching of the reaction mixture with an acylating

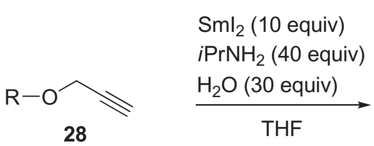
agent (trifluoroacetic acid or acetic anhydride) afforded the corresponding N-acetylated products (Table 11). This reaction sequence was adopted to avoid the difficulties in the isolation of primary amines.

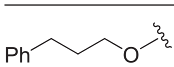
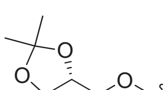
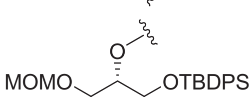
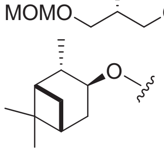
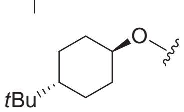
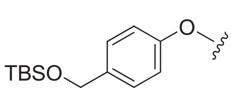
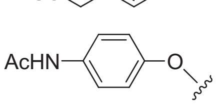
Brandi and co-workers[51] used samarium diiodide for the reductive cleavage of N-O bonds in isoxazolidines; other reagents were troublesome in this reaction. A variety of simple isoxazolidines, spirocyclopropane isoxazolidines, and spirocyclobutane isoxazolidines were readily transformed into their corresponding β-aminocyclopropanols or lactams in high yields (Table 12). Notably, the strained three- or four-membered cyclic rings of the spiro system are unaffected under these reaction conditions.

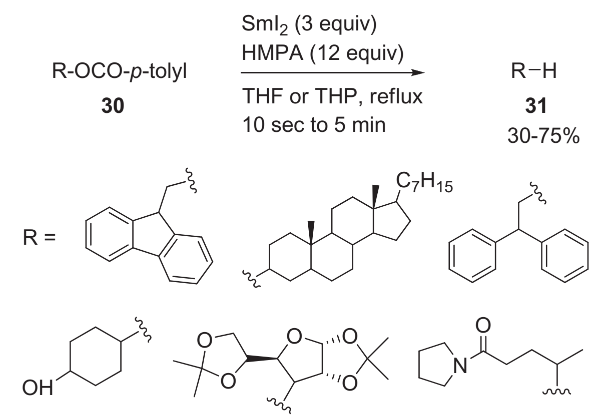
By adopting Brandi's method,[51] Ishihara and co-workers[52] employed SmI_2 to cleave the N-O bonds in chiral isoxazole derivatives **37** and **38**, which were generated from the catalytic enantioselective 1,3-dipolar cycloaddition of nitrones and propioloylpyrazoles (Scheme 18). The products were diastereoselectively converted into β-lactams **39** and **40** through reductive cleavage of the N-O bond and subsequent cyclization without any loss in enantiomeric excess.

Samarium diiodide has also been used to remove the fluorous tag in substrate **41** through reductive cleavage of the N-O bond (Scheme 19).[53] Interestingly, the terminal triple bond was unaffected after treatment with SmI_2 for 15 min in THF/MeOH at room temperature.

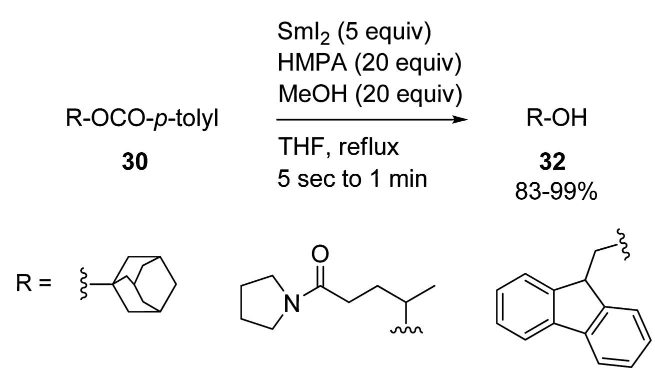
Table 9. Deprotection of propargyl ethers in various substrates.



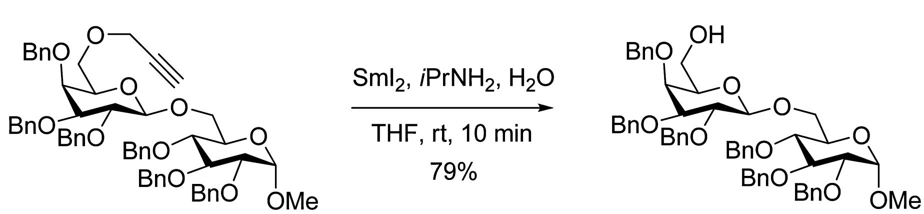
R	Time	Yield (%)
	5 min	92
	5 min	70
	10 min	93
	1 h	43
	15 min	89
	5 min	79
	15 min	68



Scheme 13.



Scheme 14.



Scheme 12.

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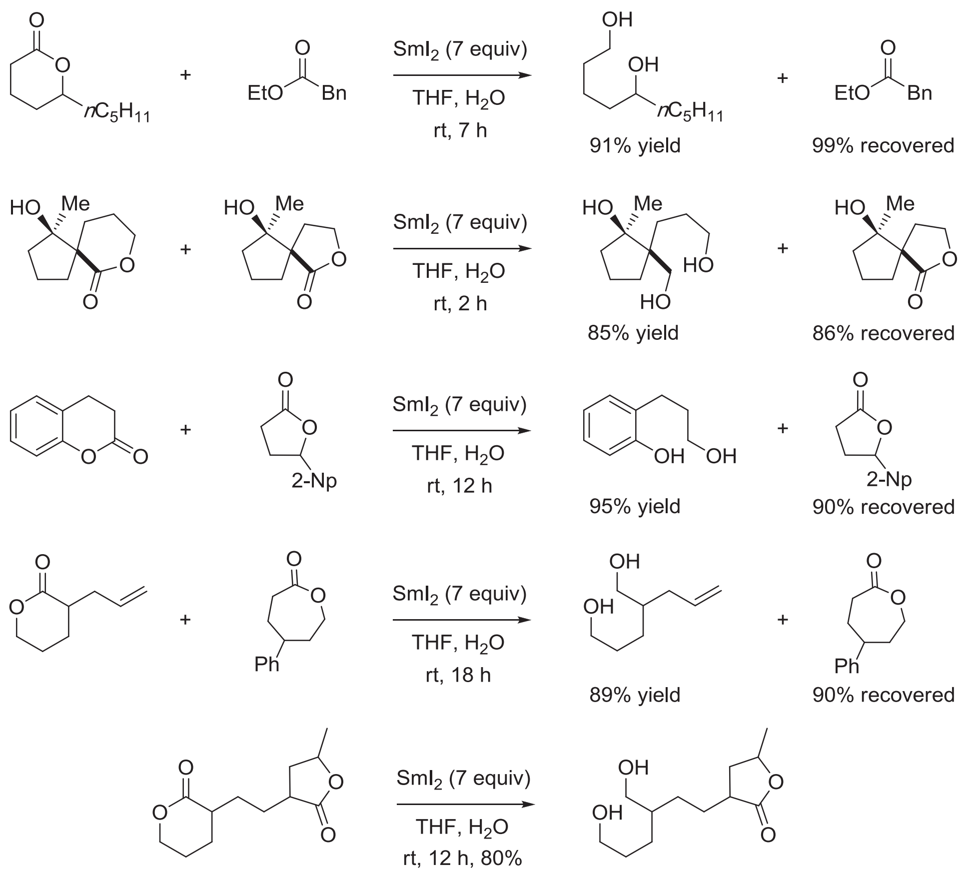
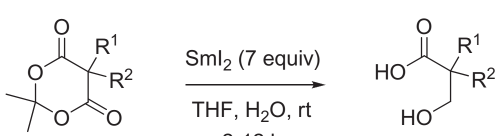


Scheme 15. Bn=benzyl, Np=naphthyl.

Table 10. Reduction of cyclic 1,3-diesters with SmI_2/water.



33 **34**

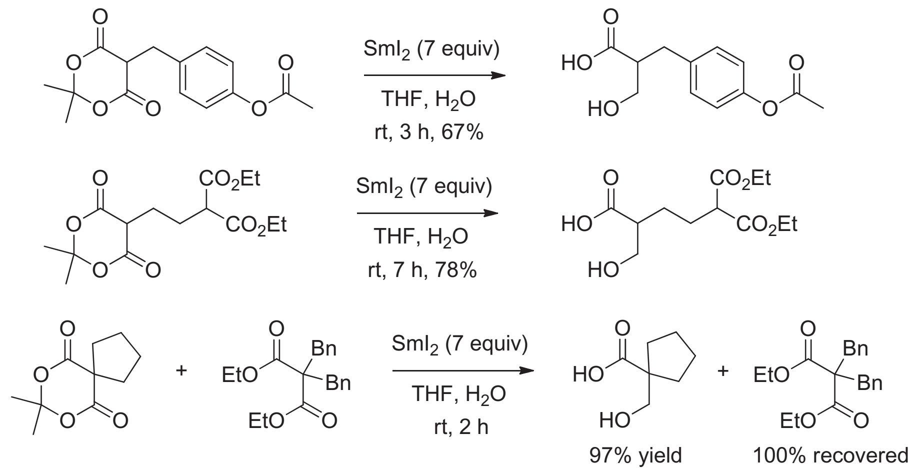
R^1	R^2	Yield (%) (**34**)
Bn	Bn	88
	-$(CH_2)_4$-	81
H	Bn	68
H	4-$MeOC_6H_4$	78
H	*i*Bu	94
Me	Bn	98

3.5. N-S and O-S Bond Fragmentations

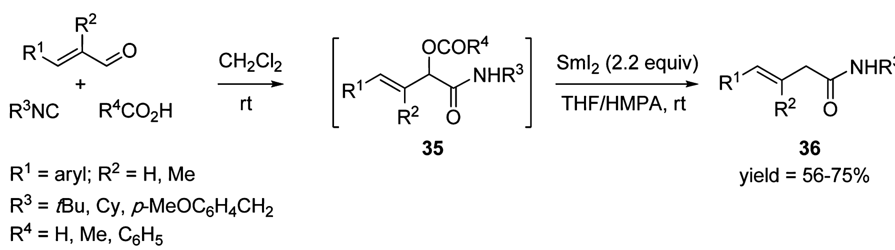
There are several reports on the deprotection of tosyl amides by using SmI_2/HMPA or SmI_2/DMPU (DMPU=1,3-dimethyl-3,4,5,6-tetrahydro-2(1H)-pyrimidinone) in refluxing THF and the deprotection of *N*-acyl *N*-tosyl amides by employing SmI_2 or SmI_2 in combination with aliphatic alcohols.[54] Recently, Ankner and Hilmersson developed the SmI_2/pyrrolidine/water procedure to cleave tosyl-protected amines (Table 13) and alcohols (Table 14) under mild conditions in almost-quantitative yields.[54] Moreover, these deprotection conditions were applied to a variety of different sulfone amides **43** to obtain their corresponding amines **44** (Scheme 20).

4. Reductive Dehalogenation

In 2004, Otaka et al. investigated the samarium diiodide mediated reductive defluorination of γ,γ-difluoro-α,β-enoates (**45**–**47**; Scheme 21) for the synthesis of (*Z*)-fluoroalkene dipeptide isosteres (**49**–**51**), which are potential dipeptide mimetics.[55] The reductive defluorination of compound **45** took place with SmI_2 in THF in the presence of *t*BuOH as a kinetic trapping agent of samarium dienolate **48**, to afford compound **49** in high yields. In the same manner, chiral

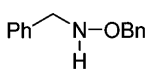
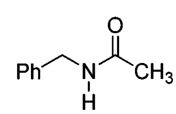
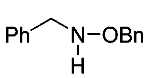
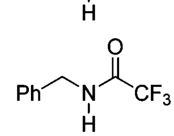
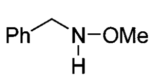
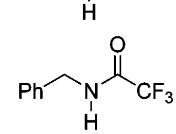
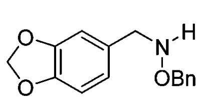
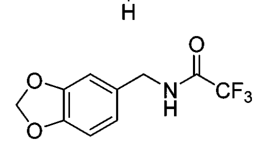
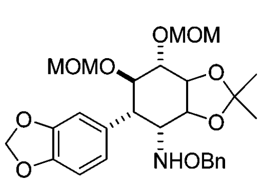
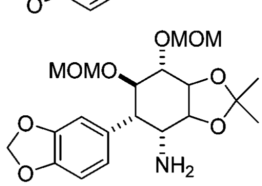


Scheme 16.



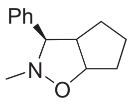
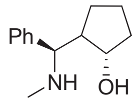
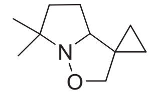
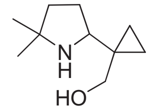
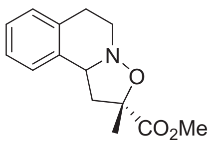
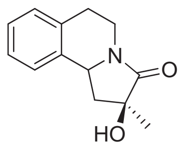
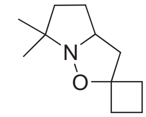
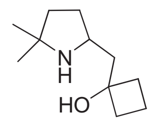
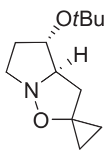
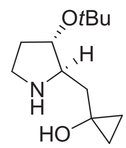
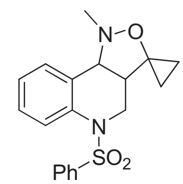
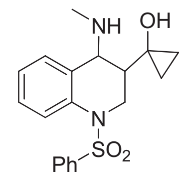
Scheme 17.

Table 11. Reductive cleavage of N-O bonds in *O*-alkylhydroxylamines promoted by SmI_2.

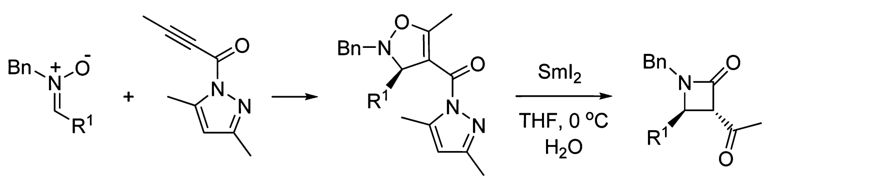
Substrate	Time (min)	Product	Yield (%)
	15		90[a]
	15		91[b]
	15		65[b]
	15		60[b]
	5 h		69[c]

[a]Quenching with acetic anhydride. [b]Quenching with trifluoroacetic anhydride. [c]Quenching with methanol.

Table 12. Cleavage of N-O bonds in some representative isoxazolidines.[a]

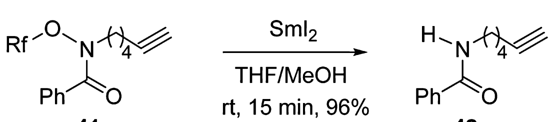
Isoxazolidine	Product	Yield (%)	Isoxazolidine	Product	Yield (%)
		98			80
		87			90
		90			95

[a]Reaction conditions: SmI_2 (3.5 equiv), THF, rt, 2 h, 1M NH_3 in MeOH, H_2O.



37 (R^1 = Ph) **39** (R^1 = Ph): 54%, >99% *de*
38 (R^1 = 3-Me-furyl) **40** (R^1 = 3-Me-furyl): 57%, >99% *de*

Scheme 18.



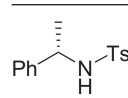
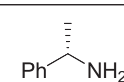
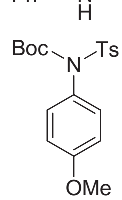
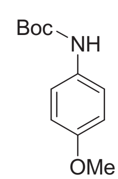
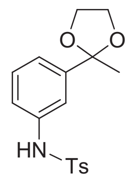
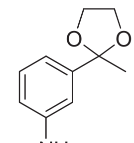
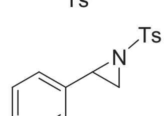
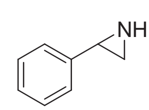
41 **42**
Rf = $C_8F_{17}CH_2CH_2CH_2$

Scheme 19.

Val-Gly-type fluoroalkene isostere **50** and Phe-Gly-type isostere **51** were synthesized by using SmI_2/*t*BuOH. Replacement of *t*BuOH by ketones or aldehydes as electrophiles provided access to α-substituted fluoroalkene isostere **52** from substrate **47**.

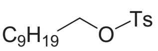
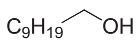
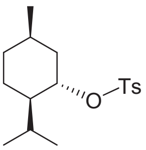
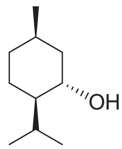
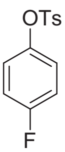
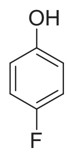
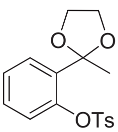
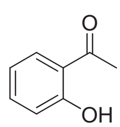
The reductive defluorination of α-fluorinated esters, amides, and thioamides were facilitated by using samarium diiodide in combination with water and Et_3N (Table 15).[56] One or more fluorine atoms were easily removed from the α positions of the carbonyl groups of esters or amides. However, fluorine atoms at other positions were unaffected. The degree of defluorination was controlled by altering the reaction temperature and the amount of amine.

Table 13. SmI_2/water/pyrrolidine-mediated cleavage of tosyl amides.

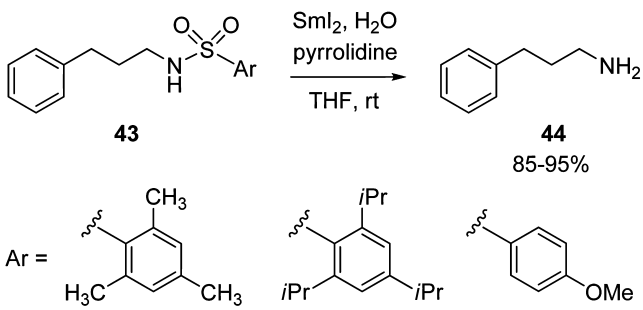
Substrate	Product	Yield (%)
		98
		94
		95
		93[a]

[a]Triethylamine was used instead of pyrrolidine.

Table 14. SmI_2/water/pyrrolidine-mediated cleavage of tosyl esters.

Substrate	Product	Yield (%)
		95
		94[a]
		95
		96

[a]100% *ee* for substrate and product.



Scheme 20.

Samarium diiodide promoted the in situ formation of a samarium enolate from chloro ester **53**; its electrophilic quenching gave *trans* adducts **54** or **55** with excellent regio- and stereoselectivity (Scheme 22).[57]

5. β-Elimination Reactions

Samarium diiodide has been widely employed to promote β-elimination reactions with high or complete stereoselectivity. Concellón and co-workers developed several β-elimination processes and reviewed the literature in 2004.[58] They showed that the β-elimination of 1-bromo-1-nitroalkan-2-ols **56** generates (*E*)-1-nitroalkenes **57** in high yields and with complete *E* stereoselectivity (Scheme 23).[59] The diastereoselectivity of the process has been explained by invoking elimination through a six-membered chelate **58** (Scheme 24).

6. Reductive Hydroxyalkylation

Huang and co-workers[60] studied the samarium diiodide mediated reductive α-hydroxyalkylation reaction[61] by using N,O-diprotected 2-pyridyl 3-pyrrolidinol-2-yl sulfide **59** as the synthetic equivalent of the chiral nonracemic α-amino synthon **60** (Scheme 25). The treatment of sulfide **59** with various ketones and aldehydes under samarium Barbier-type conditions resulted in protected *N*-α-hydroxyalkyl-3-pyrrolidines **61** with excellent diastereoselectivity at the newly formed stereogenic center in the pyrrolidine ring. Application of this method led to the formation of (2*R*,3*S*)-2-hydroxymethyl-3-pyrrolidinol (**66**) or (2*S*,3*S*)-3-hydroxyproline (**65**; Scheme 26).

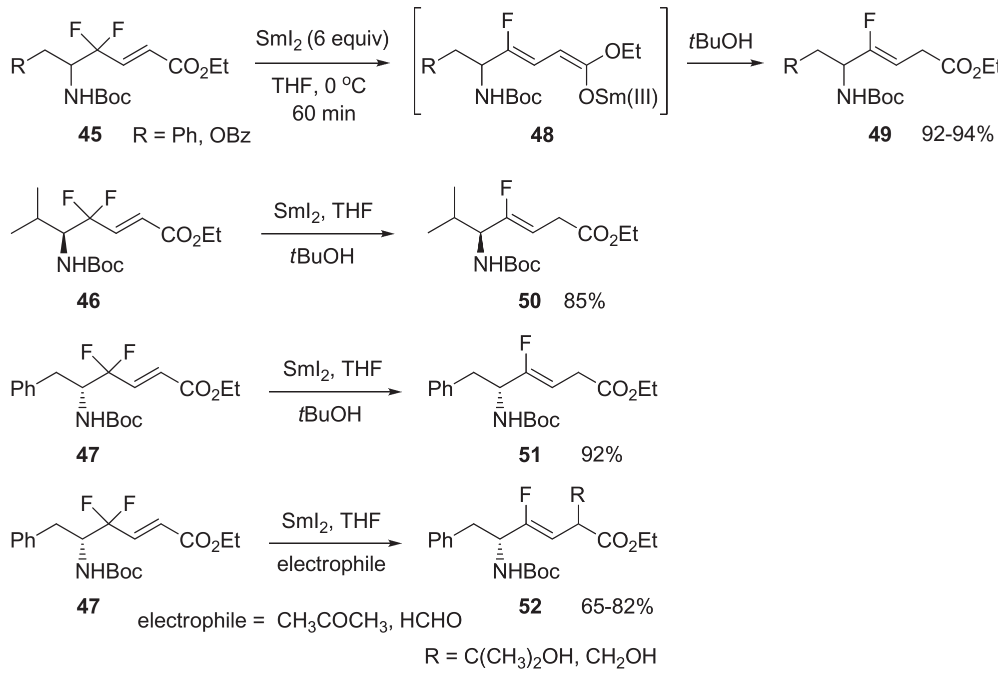
7. Reformatsky-Type Reaction

Samarium diiodide has been extensively employed in both intramolecular and intermolecular Reformatsky-type reactions.[15g,q] In an intermolecular process, highly substituted β-hydroxyketones **68** or **70** were readily synthesized from the reactions of α-haloketones **67** or **69** that contained an α′-quaternary group on the aldehydes or ketones (Scheme 27).[62] The *syn* products **68** were predominant in all of the reactions of aldehydes with α-substituted ketone **67** (R^1 = Me).

SmI_2-promoted Reformatsky reactions were employed for the preparation of β-hydroxy-γ-amino acids, such as *N*-Boc-isostatine (**74**; Boc = *tert*-butoxycarbonyl) and *N*-Boc-Dil (**78**; Scheme 28).[63] The addition of aldehyde **71** to α-chloroacetyloxazolidinone **72**, with three equivalents of SmI_2, resulted in the formation of secondary alcohol **73** as a single diastereomer. Removal of the chiral auxiliary provided *N*-Boc-isostatine (**74**) in high yield. In a similar manner, *N*-Boc-Dil (**78**) was prepared from aldehyde **75** and compound (*S*)-**76**.

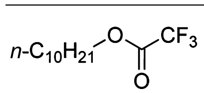
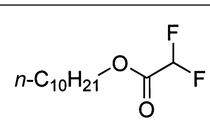
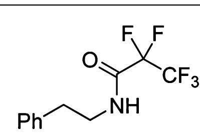
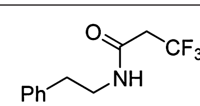
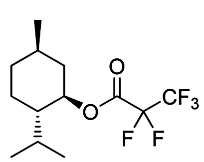
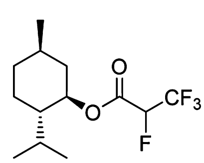
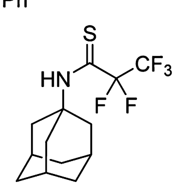
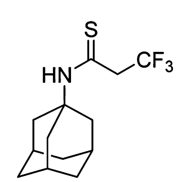
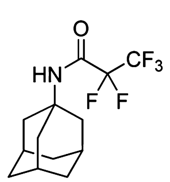
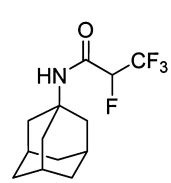
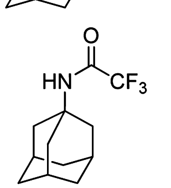
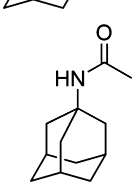
Alkyl 1-chlorocyclopropanecarboxylates **79** underwent Reformatsky-type reactions with various ketones and aldehydes in the presence of SmI_2/HMPA in THF to provide *trans*-adducts **80** or **81** in good-to-high yield and with excellent *trans* stereoselectivity (Scheme 29).[64] The acylation of carboxylates **82** with acyl chlorides also provided the corresponding acylated products in high yields. It is believed that these reactions proceed through a samarium-enolate intermediate, which only reacts with carbonyl compounds on the face *trans* to the R^2 group (Scheme 30).

Beau et al. prepared C-disaccharide building block **89**, an analogue of a carbon-linked mimic **85** of the Neu5Acα2→6GalNAcα1→OR disaccharidic component of the sialylTn antigen **84**, from 2-pyridyl sulfide **86** and aldehyde **87** by using samarium Reformatsky coupling as a key step (Scheme 31).[65] The coupling product **88** was formed in high



Scheme 21.

Table 15. Selective α-defluorination of trifluoromethyl and pentafluoropropionyl esters and amides.[a]

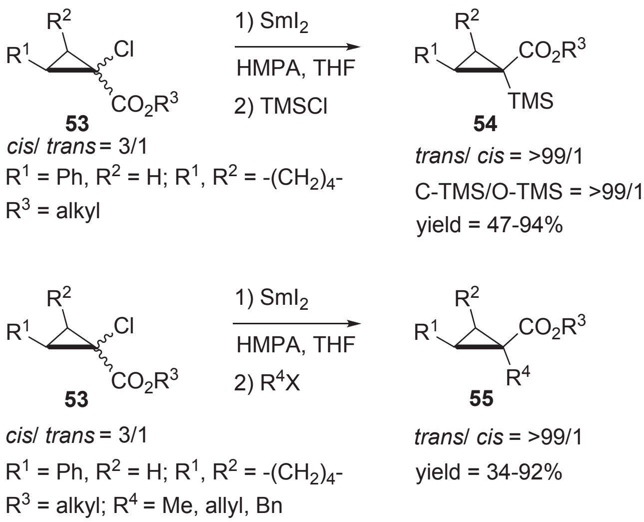
Substrate	Product	Yield (%)	Substrate	Product	Yield (%)
		30			50[b]
		82			61[b]
		75[b]			88[b]

[a]Reaction Conditions: substrate (0.3 mmol), SmI_2 (2.4 mmol), H_2O (7.2 mmol), THF, -76 °C-rt. [b]Et_3N (4.8 mmol) was added.

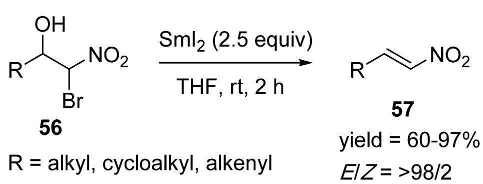
yield as a 1:1 diastereomeric mixture and was transformed into the desired C-disaccharide building block **89**.

8. Imino-Reformatsky Reaction

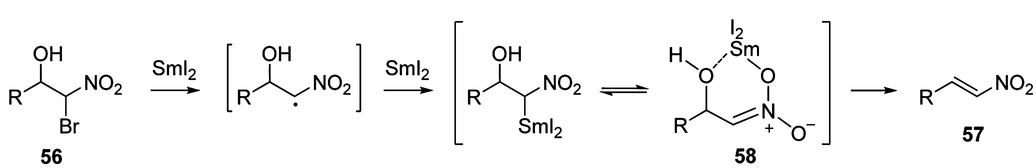
The imino-Reformatsky reaction allows easy access to β-amino acid esters from α-haloesters and imines. Recently, Ming-Hua and co-workers studied the SmI_2-promoted asymmetric addition of *tert*-butyl bromoacetate to *N*-*tert*-butanesulfinyl aldimines **90** to afford chiral β-amino acid esters **91** in good-to-high yields with excellent diastereoselectivities (Scheme 32).[66] They proposed that the samarium enolate that was generated from *tert*-butyl bromoacetate undergoes intermolecular addition to the C=N bond of the imine from the *si*



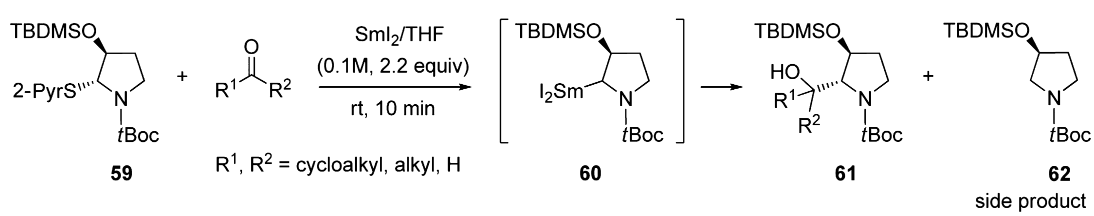
Scheme 22.



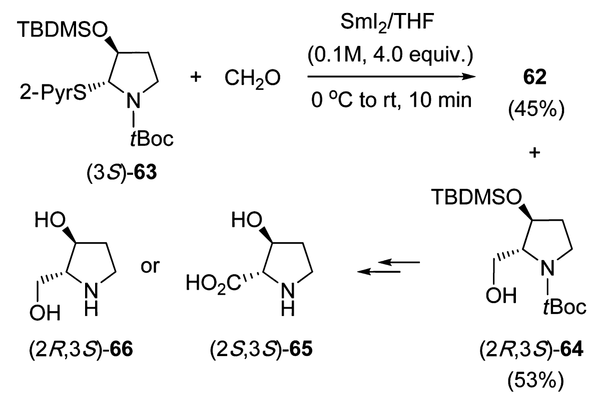
Scheme 23.



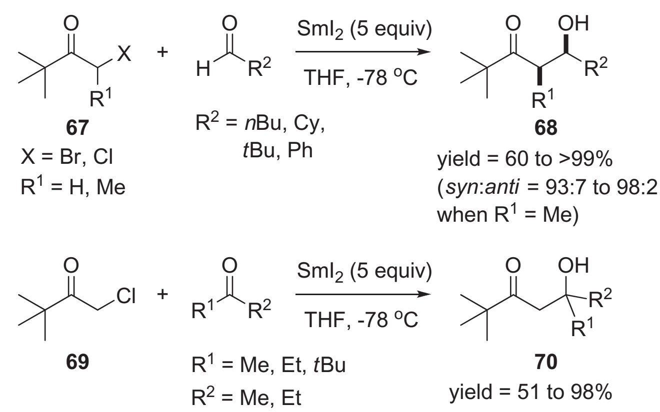
Scheme 24.



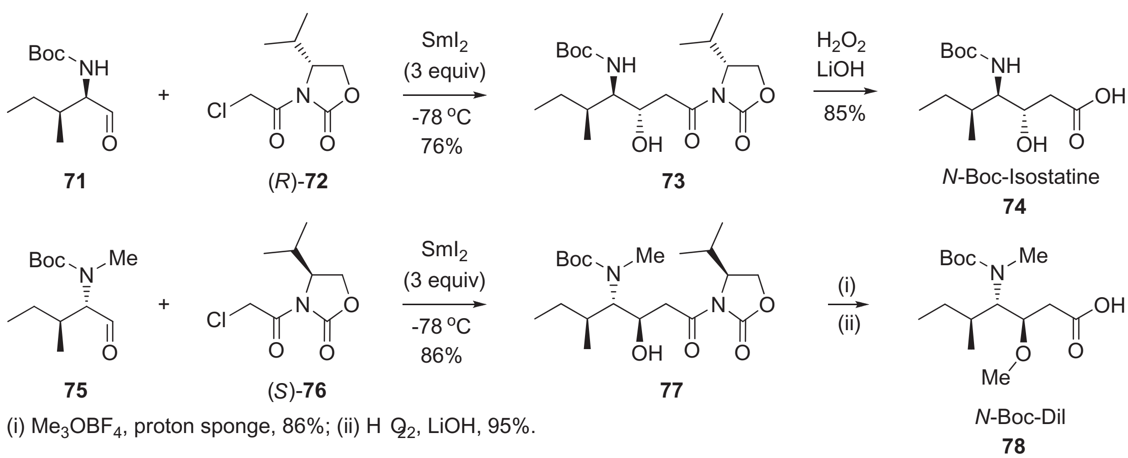
Scheme 25.



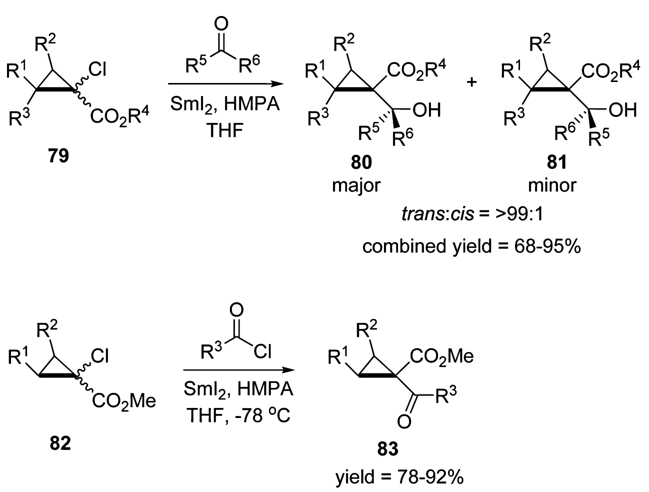
Scheme 26.



Scheme 27.



Scheme 28.

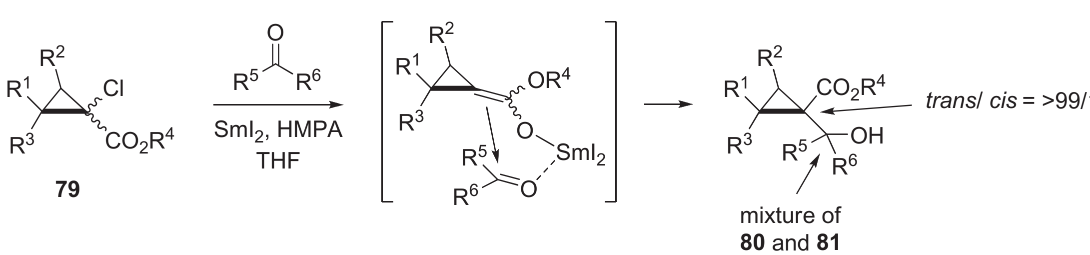


Scheme 29.

face and proceeds via a six-membered transition state **92**, thereby giving the *S* product (Scheme 33).

9. Reductive Dimerizations

The SmI_2/HMPA procedure induces the dimerization of cyclopropyl ketones through reductive cleavage of the cyclopropane, thereby leading to a variety of dimeric compounds, depending on the nature of the cyclopropyl ketone substrate.[67] Simple alkyl cyclopropyl ketones **93–95** gave their corresponding 1,8-diketones **96–98** in low-to-good yields (Scheme 34). On the other hand, the aryl-substituted cyclopropyl ketones proceeded in a more-complex fashion. In the case of substrate **99**, which contained a phenyl group at the C2 position of the cyclopropane ring, the dimerization product **100** (22% yield) was formed as a mixture with 5-phenylpentan-2-one (**101**) and styrene (**102**; Scheme 35). The formation of compound **101**



Scheme 30.

could be explained as the result of a simple reductive opening of compound **99** without dimerization, whilst an unclear fragmentation reaction might lead to compound **102**.

Indeed, the reaction of cyclopropyl phenyl ketone **103** with the SmI_2/HMPA complex formed a dimerization product **104** as the sole product in very good yield (Scheme 36). When the *para* position of the phenyl group was blocked by the bulky *tert*-butyl group, as in compound **105**, the related coupling product **106** was formed from attack of the ring-opened intermediate at the *ortho* position of the aryl moiety.

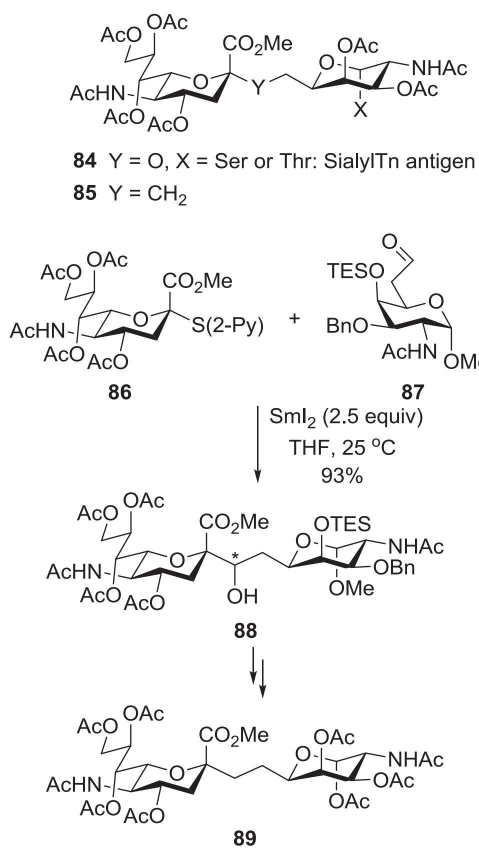
In the presence of SmI_2/HMPA reagent system, methyl 1-methylcyclopropyl ketone (**109**) furnished δ-hydroxy ketone **110** as a mixture of diastereomers in moderate yield (Scheme 37). This product is generated by the attack of a ring-opened intermediate of one molecule onto the carbonyl group of a second molecule. The reductive coupling of cyclopropyl 2-thienyl ketone (**111**) revealed another manner of dimerization, in which the product **112** retained the two cyclopropyl groups (Scheme 37).

10. α-Amination of Ketones

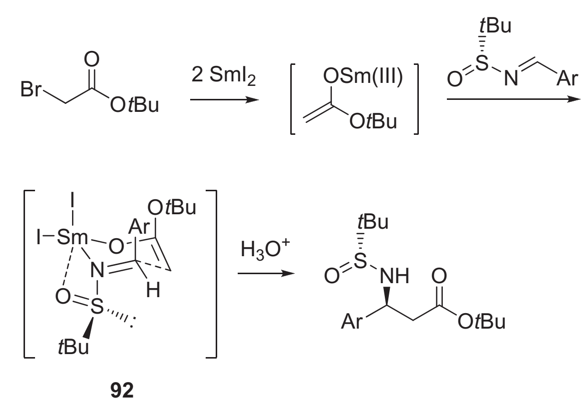
Xu, Lin, and co-workers reported the SmI_2-promoted electrophilic α-amination of cyclic and acyclic α-heterosubstituted ketones **113–115** with di-*tert*-butylazodicarboxylate (DTBAD) under mild conditions (Scheme 38).[68] These reactions proceeded regiospecifically and in high yields through a samarium-enolate intermediate.

11. Summary and Outlook

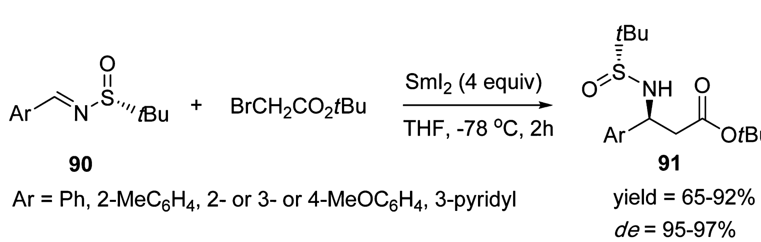
The history of the use of samarium diiodide in organic chemistry has been briefly summarized, recalling the initial contributions of our group, which led to an explosion in the number of publications from many research groups all over the world. Various types of transformations are made possible by the use



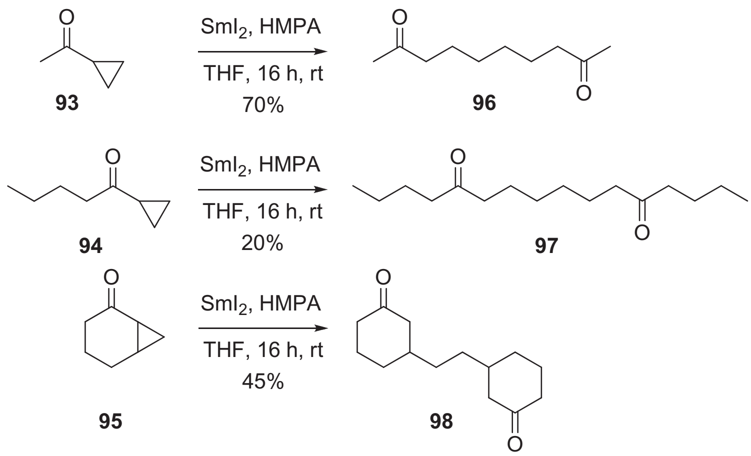
Scheme 31.



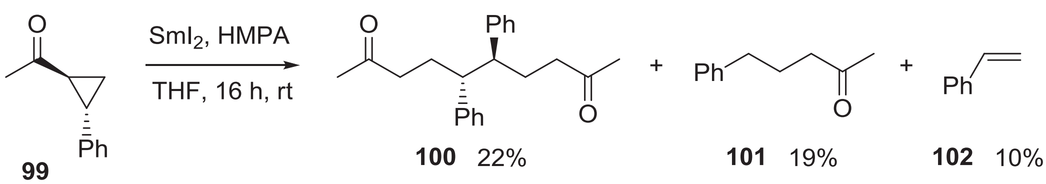
Scheme 33.



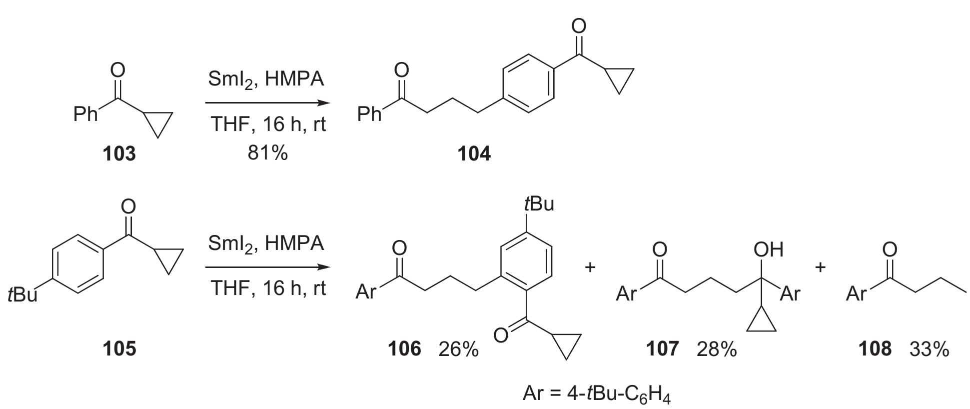
Scheme 32.



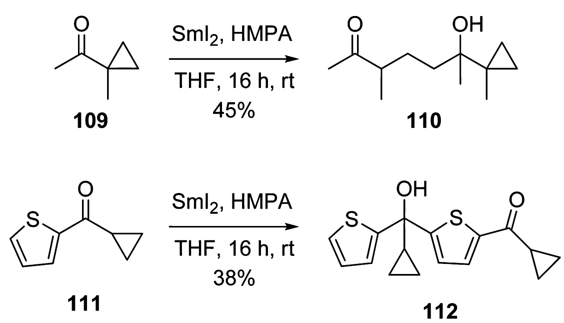
Scheme 34.



Scheme 35.



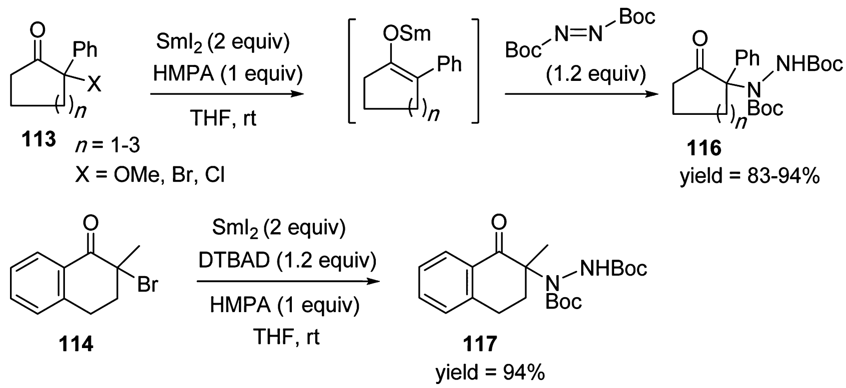
Scheme 36.



Scheme 37.

of samarium diiodide. The main review articles on the use of samarium diiodide are listed in ref. [15], which gives an idea of the importance of this reagent. Some applications in the synthesis of natural products with complex structures have also been reviewed.[15k,q]

It was not possible herein to fully describe all of the facets (synthesis and mechanisms) of Sm^{II} chemistry. Thus, we arbitrarily selected some useful results that have recently been described in literature. The reactivity of SmI_2 can be tuned by the introduction of additives, which is a powerful way to accelerate some transformations. Many of these reactions are



Scheme 38.

completely or highly selective. Most of the time, these reactions can be performed within a temperature range that is convenient for organic synthesis. Classical solvents, such as THF, are usually suitable. The compulsory conditions for good reproducibility are to avoid oxygen in the flask/solvents to prevent the formation of Sm^{III} species.

As mentioned in the Introduction, samarium diiodide initially generates radical species (Scheme 3) that are prone to subsequent evolution. Often, these reactions are quite fast under mild conditions. They are also frequently stereoselective for substrates that contain oxygen atoms because of chelation effects owing to the oxophilicity of samarium.

The main limitation of Sm^{II} chemistry lies in the difficulty in performing catalytic reactions. To overcome this drawback, Zn or Mg have been used as co-reducing agents in the presence of some silane derivatives.[69] An excess of mischmetal, a cheap industrial mixture of some lanthanide metals, has been successfully used by Namy and co-workers in the presence of catalytic amounts of SmI_2 (10%) for some reactions.[70]

The vigorous development of Sm^{II} reagents in synthesis is well reflected by the large number of papers that are devoted year after year to this area (42 publications on average per year, Scopus search for the period 2002–2011). Unconventional or unexpected transformations are often observed and will certainly be a motivation for further research and development in the future.

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